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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference DC/BR70208	FOR FURTHER ACTION See Notif	ication of Transmittal of International Examination Report (Form PCT/IPEA/416)					
International application No. PCT/FR00/01728	International filing date (day month year) 21 June 2000 (21.06.00)	Priority date (<i>day-month-year</i>) 21 June 1999 (21.06.99)					
International Patent Classification (IPC) or national classification and IPC C12Q 1/70							
Applicant	BIO MERIEUX						
This international preliminary exam Authority and is transmitted to the ap	nination report has been prepared by this plicant according to Article 36.	International Preliminary Examining					
2. This REPORT consists of a total of	6 sheets, including this cover s	sheet.					
been amended and are the ba	ied by ANNEXES. i.e., sheets of the descript sis for this report and/or sheets containing re607 of the Administrative Instructions under	ectifications made before this Authority					
These annexes consist of a to	tal of sheets.						
3. This report contains indications relati	ng to the following items:						
1 Basis of the report							
II Priority							
III Non-establishment o	of opinion with regard to novelty, inventive s	tep and industrial applicability					
IV Lack of unity of inv	ention						
V Reasoned statement citations and explan	under Article 35(2) with regard to novelty, in ations supporting such statement	nventive step or industrial applicability;					
VI Certain documents of	ited						
VII Certain defects in th	e international application						
VIII Certain observations	on the international application						
Date of submission of the demand	Date of completion of	This ranget					
05 January 2001 (05.01.		tember 2001 (11.09.2001)					
Name and mailing address of the IPEA/EP	Authorized officer						

Telephone No.

Facsimile No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/FR00/01728

I. Bas	is of th	he report		<u></u>	
1. Thi und	is repo ler Artic	rt has been drawn cle 14 are referred to	on the basis o	f (Replacement sheet as "originally filed"	ets which have been furnished to the receiving Office in response to an invitation and are not annexed to the report since they do not contain amendments.):
	\boxtimes	the internationa	ıl application a	as originally filed.	-
		the description.	pages	1-15	as originally filed.
			pages		filed with the demand.
			pages		
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		the claims.	Nos	1-5	as originally filed.
					. as amended under Article 19.
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2. The :	amend	dments have resulte			
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3.	This to go	report has been es beyond the discle	stablished as if	f (some of) the ame	tendments had not been made, since they have been considered a Supplemental Box (Rule 70.2(c)).
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4. Addit	tional	observations, if nec	cessary:		
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INTERNATIONAL PACLIMINARY EXAMINATION REPORT

International application No. PCT/FR 00/01728

Statement			
Novelty (N)	Claims	1-14	YES
	Claims		NO
Inventive step (IS)	Claims	1-14	YES
	Claims		NO NO
Industrial applicability (IA)	Claims	1-14	YES
	Claims		NO

- 2. Citations and explanations
 - 1. The following documents are referred to:
 - D1 WO-A-96/08580
 - D2 Antimicrobial Agents and Chemotherapy, 42(12), Dec. 1998, 3256-3265
 - D3 Antimicrobial Agents and Chemotherapy, 40(11), Nov. 1996, 2535-2541
 - D4 Journal of Virology, 69(9), Sept. 1995, 5431-5436
 - D5 WO-A-90/14842
 - D6 Journal of Biochemistry, **268**(15), June 1993, 11939-11945 (this document is cited by the applicant).
 - 2. D1 describes a method for determining, in a biological sample taken from a patient contaminated with HIV 1, a possible resistance of the HIV 1 viral strain to treatment with an anti-protease agent, which involves searching for the presence of at least one position in the peptide sequence associated with resistance (D1, claims). D1 mentions two mutations which are particularly effective in inducing resistance: KN55N and L90M (D1, page 45, lines 16-19).

2.1 'Similar methods are described in D2-D4:

D2 refers to the detection and identification of mutations in the peptide sequence of HIV 1 protease, which are associated with increased resistance to the anti-protease agent indinavir. The most significant mutations appear at positions 63, 84 and 90 and concern the L63P. I84V and L90M substitutions (D2: abstract).

D3 describes a method for detecting mutations in HIV 1 protease associated with resistance to protease inhibitors. The method is applied to blood samples and the mutations concern positions 10, 46, 48, 63, 82, 84 and 90 (abstract and results).

D4 describes mutations at positions 48 and 90 of HIV 1 protease which increase resistance to the anti-protease agent Ro 31-8959 (abstract).

- 2.2 The methods defined in independent Claims 1 and 8 differ from the method known from D1-D4 in that the HIV 1 strain is replaced by HIV 2.
 The subject matter of independent Claims 1 and 8 is therefore novel (PCT Article 33(2)).
- 2.3 D5 describes a vaccine against HIV containing a modified protein of HIV 2. D5 discloses inter alia a nucleic acid sequence including the sequence CCA AGA ATA suitable for use in the method claimed in the present application (D5, page 7, line 4, and page 18, line 3). However, this sequence contains more than 40 nucleotides. Furthermore, none of the cited prior art documents describes the other samples defined in independent Claims 7 and 14. Consequently, the subject matter of these claims is also novel (PCT Article 33(2)).

Form PCT/IPEA/409 (Box V) (January 1994)

- 3. The problem addressed by the present invention can therefore be considered to be that of providing a method and nucleotide samples for identifying mutations which render proteases of the HIV 2 strain resistant to antiprotease agents.
- 3.1 At-the-time-of the invention, the amino acid sequence of the HIV 2 protease would have been known to a person skilled in the art (as indicated on page 2 of the application). He would also have been familiar with the fact that the sequences of the proteases of HIV 1 and HIV 2 are relatively conserved. At first glance, it would therefore appear to be obvious for a person skilled in the art to follow the method of documents D1-D4 and, by virtue of the conservation between HIV 1 and HIV 2, to diagnose mutations in known positions, namely positions 10, 46, 48, 55, 63, 82, 84 and 90, thereby obtaining a method and nucleotide samples corresponding to Claims 1, 7, 8 and 14. However, as illustrated by D6 (summary), it was also known that even apparently slight differences between the HIV 1 and HIV 2 strains could result in major differences. For instance, mutation of a single amino acid will not provide the predicted resistance but will increase sensitivity to a protease by a factor of 100.
- 3.2 In view of these facts, a person skilled in the art could not have anticipated the present invention as defined in independent Claims 1, 7, 8 and 14 and in dependent Claims 2-6 and 9-13.

 The subject matter of Claims 1-14 is therefore inventive (PCT Article 33(3)).

INTERNATIONAL PREZIMINARY EXAMINATION REPORT

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ternational application No. PCT/FR 00/01728

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VII.	Certain	defects	in the	international	abblication

The following defects in the form or contents of the international application have been noted:

Contrary to the requirements of PCT Rule 5.1(a)(ii), the description does not indicate the relevant prior art disclosed in D1-D5, nor does it cite these documents.

Form PCT/IPEA/409 (Box VII) (January 1994)



REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

Box No. I

Box No. II APPLICANT

State (that is, country) of nationality:

State (that is, country) of nationality:

States

instead to indicate a special address to which correspondence should be sent.

This person is applicant for

the purposes of:

Name and address:

This person is applicant

for the purposes of:

International Application No.
International Filing Date
Name of receiving Office and "PCT International Application"

iving Office use only

Applicant's or agent's file reference (if desired) (12 characters maximum) DC/BR70208 TITLE OF INVENTION SEARCH METHOD FOR RESISTANCE TO ANTI-PROTEASES OF A STRAIN OF THE HIV-2 VIRUS FROM A BIOLOGICAL SAMPLE TAKEN FROM A PATIENT This person is also inventor Name and address: (Family name followed by given name; for a legal entity, full official designation. Telephone No. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) Facsimile No. **BIO MERIEUX** 69280 MARCY - L'ETOILE - FRANCE Teleprinter No. Applicant's registration No. with the Office State (that is, country) of residence: **FRANCE FRANCE** all designated all designated States except the the States indicated in the the United States United States of America of America only Supplemental Box Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) Name and address: (Family name followed by given name; for a legal entity, full official designation, This person is: The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) applicant only ASSISTANCE PUBLIQUE - HOPITAUX DE PARIS applicant and inventor 3 Avenue Victoria 75004 PARIS - FRANCE inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office State (that is, country) of residence: **FRANCE** FRANCE all designated all designated States except the United States the States indicated in the the United States of America of America only Supplemental Box Further applicants and/or (further) inventors are indicated on a continuation sheet. Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: common representative Telephone No. (Family name followed by given name; for a legal entity, full official 01 43 12 84 60 designation. The address must include postal code and name of country.) TONNELLIER Jean-Claude NONY & ASSOCIATES Facsimile No. 29, Rue Cambacérès 01 43 12 84 70 **75008 PARIS** FRANCE Teleprinter No.

Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used

Agent's registration No. with the Office

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)						
If none of the following sub-boxes is used, this sheet should not be included in the request.						
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) TELLES Jean-Noël 33, Rue Dautancourt 75017 PARIS - FRANCE	This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.)					
	Applicant's registration No. with the Office					
State (that is, country) of nationality: State (that is, country) of res FRANCE	FRANCE					
	nited States the States indicated in the Supplemental Box					
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) BRUN-VEZINET Françoise 24 Boulevard St Germain 75005 PARIS - FRANCE	This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office					
State (that is, country) of nationality: State (that is, country) of res						
	FRANCE nited States the States indicated in the Supplemental Box					
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) DESCAMPS Diane 85 Boulevard Pasteur 75015 PARIS - FRANCE DESCAMPS Diane Applicant and inventor inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office						
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1 1 1 2 1 1 2 1 1 2 1 1 2 1 2 1 2 1 2 1	FRANCE nited States					
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) This person is: applicant only applicant and inventor inventor only (If this check-box is marked, do not fill in below.) Applicant's registration No. with the Office						
State (that is, country) of nationality: State (that is, country) of residence:						
the purposes of: States the United States of America of An	the States indicated in the Supplemental Box					
Further applicants and/or (further) inventors are indicated on another continuation sheet.						



Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a): (Double-click here if you want all the boxes below checked.)

Regional Patent

- AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- EP European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

National Patent (if other kind of protection or treatment desired, specify on dotted line):

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\boxtimes	ΑE	United Arab Emirates	\boxtimes	GE	Georgia	\boxtimes	MW	Malawi
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\boxtimes	\mathbf{AM}	Armenia	\boxtimes	HR	Croatia	\boxtimes	NO	Norway
\boxtimes	AT	Austria	\boxtimes	HU	Hungary	$\overline{\boxtimes}$	NZ	New Zealand
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Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet								
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Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except the designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM							
The priority of the foll	lowing earlier application	on(s) is hereby claimed:					
Filing date	Number		Where earlier application	n is:			
of earlier application (day/month/year)	of earlier application	national application:	regional application:*	international application: receiving Office			
item (1) 21 june 1999	99 07855	FRANCE	regional Office	Tecetving Office			
item (2)							
item (3)							
item (4)							
item (5)							
Further priority cl	laims are indicated in the S	Supplemental Box.					
The receiving Office is r (only if the earlier applied Office) identified above a	cation was filed with the	ransmit to the Internationa Office which for the purpo	al Bureau a certified copy of oses of this international app	the earlier application(s) plication is the receiving			
all items [1]	tem item (2)	(3) item (4)	item item (5)	other, see Supplemental Box			
*Where the earlier applicat Industrial Property or one l	tion is an ARIPO application, Member of the World Trade (indicate at least one country Organization for which that e	y party to the Paris Convention j arlier application was filed (Rui	for the Protection of			
Box No. VII INTERNATIONAL SEARCHING AUTHORITY							
Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used): ISA /							
			arch has been carried out by or	requested from the International			
Date (day/month/year)	Number		Country (or regional Office	20)			
10 May 2000	FA 5763	97	OEB	:e)			
Box No. VIII DECLAR	ATIONS						
The following declarations at the right column the number	are contained in Boxes Nos. V of each type of declaration):	III (i) to (v) (mark the applical	ble check-boxes below and indica	nte in Number of declarations			
Box No. VIII (i)	Declaration as to the ider	ntify of the inventor		:			
Box No. VIII (ii)	Declaration as to the app and be granted a patent	licant's entitlement, as at the in	nternational filing date, to apply fo	or :			
Box No. VIII (iii)	Declaration as to the app priority of the earlier app		nternational filing date, to claim th	he :			
Box No. VIII (iv)	Declaration of inventorsh America)	nip (only for the purposes of the	e designation of the United States	s of :			
Boy No VIII (v)	Declaration of to man and	disability attention in the		_			

Box No. IX CHECK LIST; LANGUAGE OF FILING							
This international application contains: (a) the following number of sheets in	This international application is accompanied by the item(s) (mark the applicable check-boxes below and						
(a) the following number of sheets in paper form: request (including declaration sheets) : 4 description (excluding sequence listing part) : 15 claims : 3 abstract : 1 drawings : Sub-total number of sheets : sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) Total number of sheets : 23 (b) sequence listing part of description filed in computer readable form (i) only (under Section 801(a)(i)) (ii) in addition to being filed in paper form (under Section 801(a)(ii)) Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained	ritem(s) (mark the applicable check-boxes below and right column the number of each item): 1.	number, : : : : : : : : : : : : : : : : : : :					
(additional copies to be indicated under item 9(ii), in right column):	of the copy or copies with the sequence I part mentioned in left column						
	10. 🛮 other (specify) Search Report	:					
Figure of the drawings which	Language of filing of the	· · · · · · · · · · · · · · · · · · ·					
should accompany the abstract: Box No. X SIGNATURE OF APPLICANT	international application: FRENCH						
	, AGENT OR COMMON REPRESENTATIVE In signing and the capacity in which the person signs (if such ca	pacity is not obvious from reading					
Paris, 21 june 2000 NONY & ASSOCIATES Attorneys of Patent Law 29, RUE CAMBACÉRÈS TONNELLIER Jean-Claude 75008 PARIS							
	For receiving Office use only						
Date of actual receipt of the purported international application:		2. Drawings:					
 Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 		received:					
Date of timely receipt of the required corrections under PCT Article 11(2):		not received:					
5. International Searching Authority (if two or more are competent): ISA / 6. Transmittal of search copy delayed until search fee is paid							
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Date of receipt of the record copy by the International Bureau:							